-2-

Commissioner of Patents and Trademarks

09/980,163

## LISTING OF DISCLOSURE AMENDMENTS

Please replace the paragraph beginning on page 8, line 25 and ending on page 9, line 9 of the specification with the following amended paragraph:

Modules 16, 20 and 22 are linked to a property behavior models module 24 that uses experimental data, parameter interaction data and remaining significant parameters for determining an optimal mathematical model for each property which is likely to better estimate that property. The model data as generated at module 24 is fed to a property behavior relation module 26 that also receives experimental data from module 16 statistically estimate polynomial coefficients to incorporated within the established property behavior models, thereby generating a behavior relation for each property. The S-Plus statistical software from MathSoft may be used to program module 26 to apply the appropriate regression methods to the data. System 10 is further provided with a goal function module 28 linked to property weighting module 14 and property behavior relation module 26 to generate, from specified goal values for the properties, a goal function in terms of property weighted deviations between properties as estimated by the behavior relations and the corresponding specified goal values for these properties.

(b)

Please replace the paragraph on page 10, lines 6-15 of the specification with the following amended paragraph:

### Commission r of Patents and Trademarks

09/980,163

7 (h) The AHP method consists of building a hierarchical tree from all properties, with one or more hierarchical levels depending on existing relations between the properties. For each level, a pair-wise comparison matrix is built between using the properties of this level and presented at an input of the parameters weighting module 14 shown in Fig.21, which executes in step 40 in Fig. 2. For each pair-wise comparison, the normalized eigenvector is derived associated with the higher eigenvalue. The components of this eigenvector give the relative importance of each property called the local weight. Finally, the above normalized vectors are combined to find the global weight for each property.

Please replace the paragraph on page 15, lines 24-27 of the specification with the following amended paragraph:



This mathematical approach induces a reduction of the dimension of the variables, consequently we pass from "n" variables to "n-1" variables. In the actual case, we start with the most important variables from the behavior laws with the highest weight values of the factor property.

Please replace the two paragraphs on page 16, lines 1-16 of the specification with the following amended paragraphs:

# Commissioner of Patents and Trademarks

09/980,163

This approach is known under the name of network optimization, in this case the network nodes are built by the optimal values of the variable by decreasing order of the factor property's rank.

After the iterative optimization step 48 is completed, although the set of optimal parameter values  $X0_i$  obtained can generally be considered as the solution to recommend, that solution is preferably evaluated amongst other alternative solutions by following steps 50 and 52 as shown in Fig. 2. At step 50, an experimental run of the process is carried out using the obtained set of optimal parameter values, to obtain experimental values for the k properties  $Y_i$ . The optimal property parameter values X0, and associated experimental property values are then evaluated at step 52 to obtain ranking thereof amongst a number m of other alternative solutions, which may have been selected from knowledge base 12 shown This evaluation is preferably performed by a in Fig. 1. complete AHP process algorithm, using the set of k property weights  $w_j$  as previously obtained through step 40.

Please replace the paragraph beginning on page 18, line 4 and ending on page 19, line 17 of the specification with the following amended paragraph:

(A)

The nine formulations covered all of the six (6) possible combinations for the wet granulation technology and three (3) combinations of direction compression. Tablets were



- 5 **-**

manufactured by using enalapril maleate with USP/NF and EP excipients. In the direct compression technology, there is not a sufficient amount of moisture to dissolve all the drug and alkaline agent and provide for any significant neutralization reaction. However, excipients do contain a certain level of adsorbed free moisture capable of creating a microenvironment

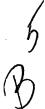
# Commissioner of Patents and Trademarks

09/980,163

where small quantities of the drug and alkaline agent can be dissolved and become available for the neutralization reaction. These phenomena could be responsible of for the appearance of physical as well as chemical stability problems and where taken into account by evaluating three (3) formulation combinations. The nine (9) formulation combinations where prepared and the tablets were stored in opened containers at 25°C/60%RH and 40°C/75%RH for a 2-week period. These open container studies are typically conducted during the early formulation development phases of a product to purposely accelerate

tree comprising properties and sub-properties:

physical and chemical changes in formulations in order to select the lead candidate, i.e., the formulation with the best stability profile. After the 2-week time period, the tablets were removed from the environmental chambers and sent to the analytical department for their performance evaluation. The performance of the formulations was determined by measuring ten (k=10) properties as a function of time and temperature, which properties were selected as follows, according to a hierarchical



-б-

### Commissioner of Patents and Trademarks

09/980,163

- Y11, Y12, Y13: % drug dissolved at 5, 15, and 30 min. (sub-properties of Y1);
  - Y2: % of cyclization product at time zero;
- Y31, Y32: % cyclization product after 2 weeks at 25°C/60%RH and at 40°C/75%RH (sub-properties of Y3);
- Y4: differential between theoretical and actual assay in mg at time zero;
- Y51, Y52: differential between theoretical and actual assay in mg after 2 weeks at 25°C/60%RH and at 40°C/75%RH (sub-properties of Y5);
- Y6: % hydrolytic product after 2 weeks at 40°C/75%.



